I. AMENDMENT

IN THE DRAWINGS

Replacement Drawing Sheet with Figure 7

Please delete the drawing sheet with Figure 7 and replace it with the replacement drawing sheet with Figure 7 that is submitted herewith.

II. REMARKS

Preliminary Remarks

Replacement drawing sheet

A replacement drawing sheet with Figure 7 is submitted. The subject matter of Figure 7 in the attached replacement drawing sheet is the identical to that of the original Figure 7; however, the text in the boxes of Figure 7 in the replacement drawing sheet is clearer and easier to read than the text of the figure that it replaces. The replacement drawing sheet does not contain new matter.

Amendment of the claims

Claims 1 and 3-5 are amended, claims 2 and 7-30 are canceled, and new claims 31-67 are submitted. No new matter has been added by virtue of the amendments or new claims. Applicants reserve the right to pursue canceled subject matter in a later filed divisional application.

Claim 1 is amended to indicate that the claimed method is performed using simulated moving bed (SMB) affinity chromatography, and that SMB apparatus comprises a plurality of modules comprising at least one solid phase comprising a ligand for which the immunoreactive compound has selective affinity, as described in the specification, *e.g.*, on page 4, lines 2-4, and page 8, lines 20-22.

Claim 1 is further amended to comprise a step of regenerating the at least one solid phase of step (a), as described in the specification, *e.g.*, on page 26, lines 14-25.

Claim 1 is also amended to include the parenthetical term "(SMB)" that identifies "SMB" as an abbreviation for "simulated moving bed."

Claim 3 is amended to depend on claim 1, in accord with the cancellation of claim 2.

Claim 4 is amended to indicate that the immunoreactive compound is dissociated from the solid phase.

Claim 5 is amended to specify that the immunoreactive compound comprises a constant region of an immunoglobulin, as described, for example, on page 7, lines 5-7.

New claims 31-67 are directed to various embodiments of the disclosed method of purifying an immunoreactive compound using SMB affinity chromatography, as described on pages 3-6 and 18-24, in the working examples (pages 24-31), and in the original claims, and as shown in the figures.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement is submitted herewith, together with the requisite fee, a Form PTO 1449 that identifies two references, and copies of the cited references.

The examiner's attention is also directed to the following two citations of which the Assignee is aware, but has been unable to obtain:

(i) G. Rossiter, "Continuous processing using solid adsorbents," presented at *Trends in Downstream Processing for Biotechnology*, organized by the Technologische Instituut in collaboration with the Dutch Biotechnology Association (NBV) (1997).

(ii) M. Bisschops, "Industrial Scale Applications of SMB Processes," presented at the *Advanced Course in Downstream Processing*, Delft University of Technology (2001).

Patentability Remarks

35 U.S.C. §112, second paragraph

Claim 19 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite in its dependence on a non-elected claim. This ground for rejection is rendered moot by the cancellation of claim 19.

35 U.S.C. §102(e) and/or 35 U.S.C. §103(a)

A) Claims 1-4, 19, 24, 25, and 28 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious in view of Ma (U.S. Patent No. 6,805,799 B2). Please note that in order to expedite examination of this application, claims 2, 19, 24, 25, and 28 are canceled, and only claims 1, 3, and 4 of the rejected claims are pending.

The Ma patent is not prior art under 35 U.S.C. §102(e)

For the reasons discussed below, the Ma patent is not available as prior art under 35 U.S.C. §102(e) or 35 U.S.C. §103(a).

U.S. Patent No. 6,805,799 B2 of Ma issued on October 19, 2004, from U.S. Patent Application No. 10/375,987, which was filed on March 1, 2003, and which claims priority benefit of U.S. Provisional Application No. 60/436,104, filed on **December 21, 2002**.

The present application was filed on September 12, 2003, and properly claims the benefit under 35 U.S.C 119(e) of the filing date of U.S. Provisional Application No. 60/410,506, which was filed on **September 13, 2002** ("the '506 application"). The filing date of the '506 application, the benefit of which is claimed by the present application, is earlier than the priority filing date of the Ma patent.

The claimed invention is fully described by the specification of the '506 application, a copy of which is attached hereto as Appendix A. Supportive description of the claimed invention is found throughout the specification of the '506 application. Steps (a)-(e) of the method of claim 1 are described in the '506 application, *e.g.*, on page 2, lines 19-29, and on pages 24-28; and SMB affinity chromatography, including the use of protein A or Protein G ligand as specified in claims 5, 50, and 60, is described in the '506 application, *e.g.*, on page 16, lines 2-13. Support for the claimed method wherein the SMB chromatographic system comprises an association zone, a wash zone, an entrainment rejection zone, an elution zone, a regeneration zone, or a re-equilibration zone, as specified in claims 38-48, 52-54, is found in the '506 application, *e.g.*, on pages 2-6 and 17-23, and in the examples on pages 24-30. Support for the method of claim 58, wherein the SMB apparatus comprises a plurality of modules, is found in the '506 application, *e.g.*, on page 6, lines 10-11. High and low salt washes as specified in claims 40, 41, 63, and 64, are described, for example, on page 23, lines 1-11. Regeneration buffer comprising urea as specified in claims 35 and 55 is described in the '506 application, *e.g.*, on page 25, lines 21-24; and CIP solution, *e.g.*, comprising phosphoric acid, as specified in claims 36, 37, 46, 47, 56, and 57, is described in the '506 application, *e.g.*, on page 25, line 25, to page 26, line 2, and in figures 8 and 9. Support for the method of claims 33, 51, and 67 wherein the concentration of immunoreactive compound in the product stream is greater than the concentration of immunoreactive compound in the initial fluid mixture (feed) is found in the '506 application, *e.g.*, on page 29, line 15, to page 30, line 1. Support for the method of claims 39 and 62 wherein effluent from a module in a wash zone is fed back into a module in the association (adsorption) zone is found in the '506 application, *e.g.*, on page 19, lines 29-30. Support for the method of claims 42 and 65 wherein solution containing purified immunoreactive compound from the product stream is introduced into a module in an entrainment rejection zone prior to elution of immunoreactive compound from

said module the elution zone is found in the '506 application, *e.g.*, on page 23, lines 11-16. Support for the method of claims 43 and 66 wherein elution wash buffer is introduced into a module an elution wash zone is found in the '506 application, *e.g.*, on page 20, lines 27-30. Identification of an immunoreactive compound that can be purified by the claimed invention as an antibody, an antibody fragment, a domain-deleted antibody, an antibody linked to a moiety capable of binding specifically to another molecule, and a fusion protein comprising a region of an immunoglobulin polypeptide fused to a polypeptide capable of specific binding to a ligand, as specified in claims 31, 32, 49, and 59, is found in the '506 application, *e.g.*, on page 7, line 5, to page 8, line 2.

From the description of the claimed invention in the specification of the '506 application, it is clear that the applicants invented the claimed invention prior to September 13, 2002, the date that the '506 application was filed in the U.S. Patent and Trademark Office. Under 35 U.S.C. 102(e), "a person shall be entitled to a patent unless the invention was described in ... a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent ..." (emphasis added - the full text of 35 U.S.C. 102(e) is printed on page 2 of the official action). Since the applicants invented the claimed invention prior to September 13, 2002, which is the filing date of the '506 application, whereas the earliest U.S. filing date for which Ma patent claims priority benefit is December 21, 2002, the Ma patent is not prior art under 35 U.S.C. §102(e).

Determination of obviousness under 35 U.S.C. §103(a) is made with regard to the prior art at the time the claimed invention was made. Since the Ma patent was not prior art under any provision of 35 U.S.C. §102 at the time that the claimed invention was made, it cannot be regarded as prior art under 35 U.S.C. §103(a).

In view of the foregoing, withdrawal of the rejection of claims 1, 3, and 4 under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious in view of Ma (U.S. Patent No. 6,805,799 B2), is respectfully requested.

B) Claims 5, 7-8, 22, 26, 27, and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ma, in view of either Stipanovic *et al.* (U.S. Patent No. 6,572,767 B2) or Hammen (U.S. Patent No. 5,240,602) and Priegnitz *et al.* (U.S. Patent No. 5,645,729). Please note that in order to expedite examination of this application, claims 7-8, 22, 26, 27, and 30 are canceled, and only claim 5 of the rejected claims is pending.

The Ma patent, cited as the primary reference, is not available as prior art under 35 U.S.C. §103(a), as discussed above. Priegnitz *et al.* describes a method of using SMB chromatography to purify small organic compounds wherein the stationary phase interacts only weakly with the adsorbed materials. For example, see col. 3, lines 45-48, and col. 4, lines 2-23, and claim 1 of the patent. Stipanovic *et al.* teaches that Protein A and Protein G may be used as an affinity ligands for purification of antibodies (*see* col. 2, lines 6-9), and Hammen similarly teaches that Protein G may be used as an affinity ligand in the purification of antibodies (col. 7, lines 8-10). The examples of chromatographic methods described by Stipanovic *et al.* and Hammen are conventional, batch-type methods; for example, *see* columns 11-14 of Stipanovic *et al.*, and columns 18-22 of Hammen. Neither Stipanovic *et al.* nor Hammen describe or suggest performing Protein A or Protein G affinity chromatography in a simulated moving bed chromatographic system.

To establish a *prima facie* case of obviousness, the prior art references themselves or the knowledge generally available to one of ordinary skill in the art must provide some suggestion or motivation to modify the reference or to combine reference teachings to obtain the claimed invention, they must teach or suggest all of the claim limitations, and they must provide a reasonable expectation that the claimed invention can be made or used successfully. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

As noted above, Priegnitz *et al.* describe the SMB chromatography system of their invention as being suitable for separating small organic compounds that interact only weakly with the stationary phase. At the time the invention was made, one of ordinary skill in the art would have recognized that chromatographic methods for separating small organic molecules are not readily adaptable to chromatographic separation of a complex mixture of proteins, due to the structural and functional differences between small organic molecules and proteins. For example, it was well known that macromolecules require significantly more time to come to adsorption equilibrium with the solid phase of a chromatographic column than small organic molecules; and that a mixture of proteins is more likely to aggregate and clog a column when present in high concentration than a mixture of small organic molecules. Therefore, one of ordinary skill in the art would not reasonably have expected that a SMB chromatography system suitable for separating small organic compounds could be modified to be suitable for successful separation of proteins without considerable experimentation and

inventive effort. Moreover, at the time the invention was made, one of ordinary skill in the art would have known that the affinity with which antibodies interact with Protein A and Protein G ligands is relatively strong and specific, unlike the weak interaction of compounds with the stationary phase of the SMB chromatography system described by Priegnitz *et al.* Accordingly, one of ordinary skill in the art would have reasonably considered the SMB chromatography system described by Priegnitz *et al.* to be unsuited for adaptation to perform Protein A or Protein G affinity chromatography for the purification of immunoreactive compounds such as antibodies, and would have had no motivation to combine the teachings of the cited references to obtain the claimed invention. In view of the foregoing, withdrawal of the rejection of claim 5 as being unpatentable over Ma, in view of either Stipanovic *et al.* or Hammen, and Priegnitz *et al.* is respectfully requested.

C) Claim 6 was rejected under 35 U.S.C. §103(a) as being unpatentable over Ma, in view of either Stipanovic *et al.* or Hammen and Priegnitz *et al.* as applied to claim 5 above, and further in view of Garrone *et al.* (U.S. Patent No. 5,959,085).

The Ma patent is not available as prior art under 35 U.S.C. §103(a), and the invention of claim 5 would not have been obvious to one of ordinary skill in the art in view of either Stipanovic *et al.* or Hammen and Priegnitz *et al.* as applied to claim 5 in the official action, for the reasons discussed above. Column 8 of Garrone *et al.* describes using an acidic buffer to remove an antibody from a chromatographic column containing Protein G or anti-IgG antibody as an affinity ligand, as pointed out on page 4 of the official action. Like the Stipanovic *et al.* and Hammen patents, Garrone *et al.* describes conventional, batch-type chromatographic methods, but does not describe or suggest performing Protein A or Protein G affinity chromatography in a simulated moving bed chromatographic system. Garrone *et al.* therefore would not have remedied the above-discussed deficiencies of the cited references as prior art under 35 U.S.C. §103(a), with respect to the patentability of either claim 5 or claim 6. Withdrawal of the rejection of claim 6 as being unpatentable over Ma, in view of either Stipanovic *et al.* or Hammen, and Priegnitz *et al.*, further in view of Garrone *et al.*, is therefore respectfully requested.

IV. IN CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: March 13, 2006

By _____

Thomas A. Cawley, Jr., Ph.D.
Reg. No. 40944
Tel. No. 703.770.7637
Fax No. 703.770.7901

PILLSBURY WINTHROP SHAW PITTMAN LLP
P.O. Box 10500
McLean, VA 22102
703.770.7900